The biological effect of the endodontic bioactive cements fast set NeoMTA plus and ProRoot-MTA on osteogenic differentiation of mesenchymal stem cells: A systematic review

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Abstract
Background and Objective: Mineral trioxide aggregates (MTA) is the standard material used in endodontic treatment and different dental specialties as pulp capping, repair for root perforation, retrograde filling restoration, apexification and/or revascularization. The aim of this systematic review is to assess the osteogenic activity of NeoMTA Plus in compared with ProRoot-MTA using mesenchymal stem cells.
Material and Methods: Two automated databases (Google Scholar and PubMed using English-language literature) were used for this systematic review. The electronic search was done in December 2018 and updated in April 2019.
Results: Our inquiry uncovered nine studies that met the exclusion and inclusion criteria. These studies investigated the osteogenic activity of NeoMTA Plus in compared with ProRoot-MTA using mesenchymal stem cells. Most of investigations in this review showed the ProRoot-MTA had a greater osteoinductivity and induced the gene expression by different MSCs exposed to it.
Conclusion: Both NeoMTA Plus and ProRoot-MTA had osteogenic activity when used as endodontic repair material.

Keywords: Bioactivity, NeoMTA, ProRootMTA, Mesenchymal stem cells, Osteogenic differentiation.

Introduction
Mineral trioxide aggregates (MTA) is the standard material used in endodontic treatment and different dental specialties as pulp capping, repair for root perforation, retrograde filling restoration, apexification and/or revascularization. Due to its handling difficulty and prolonged setting, an accelerator has been added for its improvement, although it had a negative impact on its biocompatible properties.[1] Accordingly, new fast setting NeoMTA Plus has been advocated in the market. It is a powder/gel system of tricalcium silicate-based bioactive cement. Like conventional MTA, it has nearly similar composition with varying amount of aluminum, sulfate and zirconium oxide with addition of tantalum oxide.[2-4]

Based on the prolonged setting time and handling difficulty of conventional MTA (ProRoot-MTA), fast setting NeoMTA Plus was developed to offer its bioactive and osteogenic potential. It was reported that there was some variation of their constituents as NeoMTA Plus contained higher aluminum and sulfur than conventional MTA that might interfere with its biological behavior.[4-6] There has been scarcity of studies evaluating their biocompatibility and bioactivity. In a previous studies, the evidence of bioactivity of NeoMTA Plus was reported as the calcium phosphate crystals precipitated on the material surface.[3,5] The mesenchymal stem cells (MSCs) are multipotent cells, they are capable of in vitro differentiation into various non mesenchymal lineages such as calcified-forming cells including osteoblasts-, cementoblasts- and/or odontoblasts-like cells.[7,8] MSCs were proved to have high rate of proliferation with possible growth regulation,[9] and to effectively evaluate the osteogenic potential of dental repair materials.[10]

There was a paucity of researches related to both materials in their biocompatibility and osteogenic potential. However, few studies have investigated NeoMTA Plus in compared with ProRoot-MTA materials when applied on Mesenchymal stem cells (MSCs) to induce gene expression related to osteogenic activity of stem cells. Consequently, this reviews aim was to collect all updated and available studies including imperative information concerning the effect of NeoMTA Plus on gene expression related to osteogenic activity in mesenchymal stem cells (MSCs) compared with ProRoot-MTA.

Material and Methods
This review was reported in accordance with the PRISMA statement.

Focused Question
"Is NeoMTA Plus better than ProRoot-MTA in it bioactivity on stem cells, and it ability to induce osteogenic differentiation when used as a root repair material or No?".

Search Strategy
Systematic way was performed to look-up for relevant information through several literatures & search engines with a great concern to the main question. Such study was accomplished in December 2018 and applauded with new information's until April 2019. A web search was done through PubMed (2008-2018) and Google Scholar (2008-2018) with MesH terms and/or in various combinations ("Mesenchymal Stem Cells", "Root Repair Materials", "Mineral Trioxide Aggregates", "Osteogenic Gene Expression", "Calcium Silicate Cement", "NeoMTA", and "ProRootMTA.").

Inclusion Criteria

1. Native research released in the English language.
2. Time framed articles released within 10 years from 2008 - 2018.
3. Studies carried out on human subjects only.

Exclusion Criteria

1. Articles that described the osteogenic activity of Mesenchymal Stem Cells by different dental materials excluding NeoMTA and ProRoot MTA.
2. Articles that discussed osteogenic activity of Mesenchymal Stem Cells by percentages and samples taken from animals.
3. Review articles.

Relevant articles had been red & assessed by the introduction of the close meaning ideas by the study reviewers. Full articles were obtained for most of the titles and abstracts that met the inclusion criteria, full text was accessed. From each included article, Study design, population, interventions and controls, and findings were extracted. Articles used were categorized into two main groups (free & restricted). Free ones have been downloaded directly by the URLs generated from database. The restricted group has been downloaded by the institutional access of KAU library. Even though some articles weren't mach the main idea, they have been reviewed again & decided to be either relevant or irrelevant. Even the reference was examined to identify any studies that haven't been covered by the electronic searches. A summary of this review search strategy was summarized in [Fig. 1].

Results

Our exploration uncovered nine studies which met the exclusion and inclusion criteria. These studies investigated the osteogenic activity of NeoMTA Plus in compared with ProRoot-MTA using mesenchymal stem cells. All the studies included in this systematic review were "In vitro study".[6,7,11-17] All the selected articles used different types of stem cells. Also, it used NeoMTA, ProRoot-MTA or both MTA materials with different dental materials as a root repair material. Most of investigations in this review showed the ProRoot-MTA had a greater osteoinductivity and induced the gene expression by different MSCs exposed to it.[11,12,14,15] On the other hand, Both NeoMTA and ProRootMTA have the ability to induce the expression of osteogenic markers.[6,13] All included studies were summarized in [Table 1].

Table 1: Summary of all included studies in this systematic review.

Authors/Study Design	Year	Type of MTA Used	Type of Stem Cells Used	Main Conclusion
Neha Sultana, et al, India, (In vitro study)	2018	"ProRoot MTA" + "Biodentine"+ "EndoSequence Root Repair Material (ERRM)"	"Human Bone Marrow derived Mesenchymal Stem Cells"	It seems to be these materials shown high significant osteogenic potential.
Atari Maher, et al., Spain, (In vitro study)	2018	"ProRoot MTA" + "Biodentine" + "Portland cement (Med-PZ)"	"Dental Pulp Pluripotent-Like Stem Cells"	All the 3 cements enhanced cell proliferation and osteogenic capacity with prospective potential.
Rodrigues EM, et al., Brazil, (In vitro study)	2017	"Set MTA Plus (MTA P)" + "MTA Angelus"	"Human dental pulp cells"	MTA and MTA Plus were increased mineralization processes and induced the expression of osteogenic markers.
Tomas Catala CJ, et al., Spain, (In vitro study)	2017	"MTA-Angelus" + "MTA Repair HP" + "NeoMTA Plus"	"Human dental pulp stem cells"	All the 3 materials were associated with biological effects on hDPSCs.
Ian Chen, et al., USA, (In vitro study)	2016	"RRM" + "ProRoot MTA"	"Human bone marrow mesenchymal stem cells", "periodontal ligament stem cells", and "dental pulp stem cells"	Both materials are biocompatible and promote cell proliferation and survival in an ERK-dependent manner.
Suzan Margunato, et al., Turkey, (In vitro study)	2015	"ProRoot MTA" + "Biodentine" + "MM-MTA"	"Human Alveolar Bone Marrow Stem Cells"	All the 3 materials shown the osteogenic differentiation potential of hBMSCs.
Saeed Asgary, et al., Iran,	2014	"Mineral trioxide	"Human Dental	Both materials can induce

(In vitro study)		aggregate (MTA)" + "Calcium-enriched mixture (CEM)"	Pulp Stem Cells"	osteo-/odontogenic-like phenotype differentiation of human DPSCs.
Bin-Na Lee, et al., South Korea, (In vitro study)	2014	"MTA"+ Bioaggregate"+ "Biodentine"	"Mesenchymal Stem Cells"	All the 3 materials have effects on osteoblast differentiation in mesenchymal stem cells, suggesting that these cements may be useful for root-end filling material.
Hidefumi Maeda, et al., USA, (In vitro study)	2010	"MTA"	" Human Periodontal Ligament Cells"	The human periodontal ligament cells cocultured directly with MTA upregulated BMP2 expression and calcification.

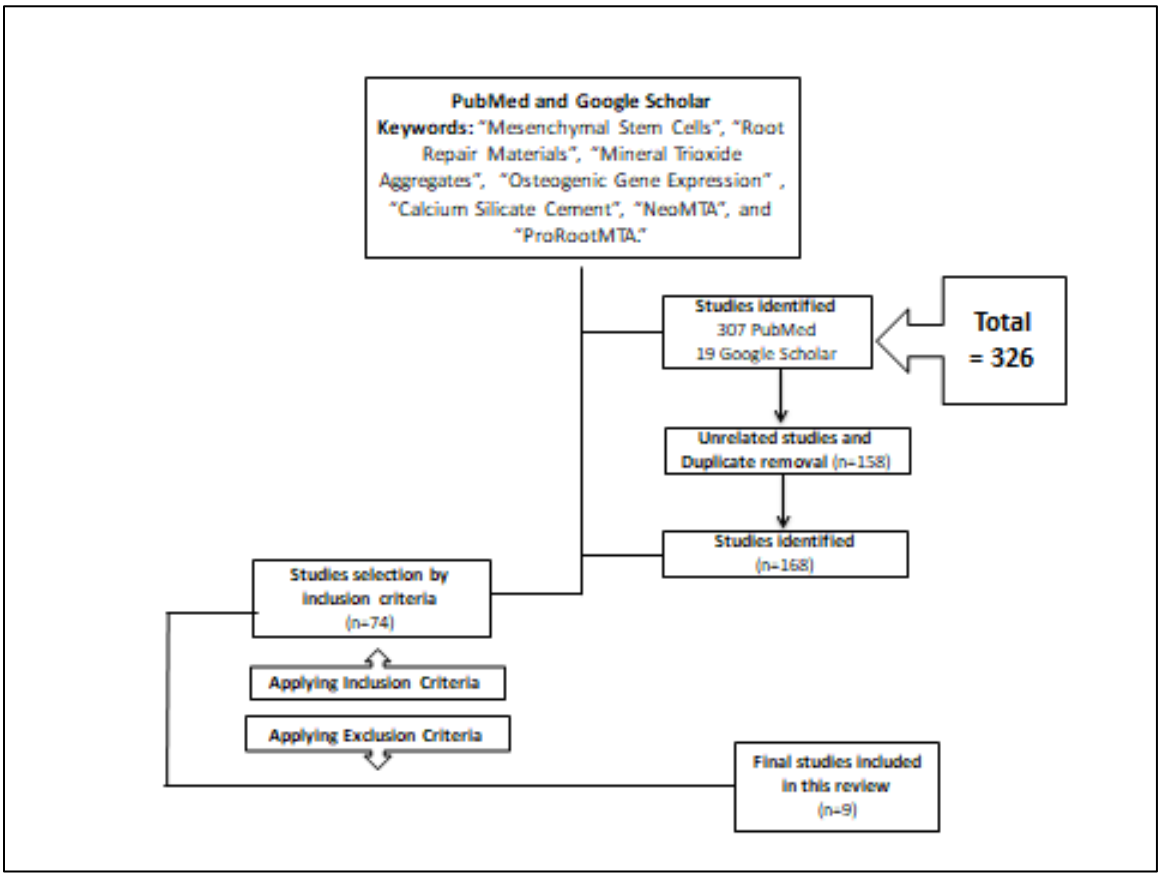

Fig. 1: Flow Chart of the Search Strategy used in this Systematic Review.

Discussion

Systematic review conducted to summarize, locate, appraise and synthesis all high quality research evidence scientific experimental studies relevant to scientific research question. The question of this review is "Is NeoMTA Plus better than ProRoot-MTA in it bioactivity on stem cells, and it ability to induce osteogenic differentiation when used as a root repair material or No?". This review use an electronic search only and the result limited to articles that can found a full article. Furthermore, the current review included 9 studies that assess the osteogenic activity of NeoMTA Plus and ProRoot-MTA using mesenchymal stem cells.

The mechanisms of osteogenesis related to NeoMTA Plus repair material have not been fully understood. To elucidate its effects, the viability, morphology, growth, proliferation and differentiation of MSCs were evaluated in the selected articles of this review. The viability of cells with progressive growth and proliferation has been indicative of the favorable therapeutic effect of repair material used.[18] However, different studies discussed the association between the ProRootMTA and cell proliferation. The findings were reported the ProRoot-MTA has the potential to induce proliferation and osteogenic differentiation of Human Bone Marrow-derived

Mesenchymal Stem Cells,[11] Dental Pulp Pluripotent-Like Stem Cells,[12] periodontal ligament stem cells,[14] Human Alveolar Bone Marrow Stem Cells.[15] Also, one study[6] investigated 3 different repair materials and found both repair materials (NeoMTA and ProRoot-MTA) have biological effects on human dental pulp stem cells in terms of cell proliferation, morphology, migration and attachment. Bone formation or bone repair has been a complex process based on the differentiation of MSCs present in pulp, periapical and/or periodontal tissues into osteoblast-like cells in association with the expression of different staged osteogenic-related factors and several genes[19] under suitable environment and/or therapeutic effect of repair material to generate calcified deposits, and repair the root defects.[7,17,20]

In the present review, Different studies investigate the association between MTA and BMP-2 gene expression and discussed how the MTA can enhance the gene expression of BMP-2. Rodrigues EM, et al. study at 2017[13] determined that co-cultures of MTA and MTA Plus with human dental pulp cells induced the expression of osteogenic markers of bone morphogenetic protein 2 (BMP-2), osteocalcin (OC) and alkaline phosphatase (ALP). The calcium silicate-based material including MTA to induce significant upregulation of BMP-2 gene expression in human periodontal cells.[7] This confirms the BMP-2 is the most osteo-inductive factor,[21] regulating cell differentiation and proliferation.[16] Maeda H, et al. study at 2010[7] determined that cocultures of MTA with human periodontal ligament cells induced early upregulation of BMP-2 gene expression through calcium sensing receptor stimulation. This stimulation could attribute to increase the extracellular calcium ion that released from MTA into culture media.[7] The differentiation process can be enhanced not only by BMP-2 but also by increasing the expression of various pro-mineralization genes like alkaline phosphatase concentration and non-collagenous matrix proteins like bone sialoprotein, osteopontin and osteocalcin[20] that are responsible for bone deposition and maturation process.[22] In study for Asgary S, et al.[16] they found the increase of alkaline phosphatase production at day seven might be attributed to its ability to initiate mineralization by supplying phosphate during cyto-differentiation stage as it has been encoded by differentiated osteoblasts and enhanced bone turnover.[17] In regarding to the expression of alkaline phosphatase, osteopontin and osteocalcin by both endodontic repair materials that evaluated in this review. The finding was reported these expression were higher in day one than that of third and seventh days due to pH-changes during setting reaction.[17] Furthermore, the release of calcium ions from MTA upregulated the biologic marker including BMP-2, alkaline phosphatase, bone sialoprotein and octeocalcin.[7,17]

In this systematic review, Most of the included articles showed the bone-related genes expression by MSCs exposed to either NeoMTA Plus or ProRoot-MTA indicated their ability to induce osteogenic activity. Also, the ProRoot-MTA had a greater osteogenic potential as it induced higher gene expression than that obtained by NeoMTA Plus.

Conclusion

The present systematic review provides concrete evidence to show biological effects of ProRoot-MTA as compared to NeoMTA on the undifferentiated mesenchymal stem cells that differentiated to osteoblast-like cells. Furthermore, clinical trials are required to examine the osteogenic activity and may provide valuable information about the NeoMTA Plus and ProRoot-MTA as endodontic repair material.

Conflict of Interest: None.

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